September 6, 2000

TANNING
RESEARCH
LABORATORIES, INC.

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Docket No. 78N-0038
Dockets Management Branch(HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20857

Dear Sir/Madam:

Tanning Research Laboratories, Inc.(TRLI) is a manufacturer of sunscreen products sold in the United States, one of the most recognizable brands being Hawaiian Tropic™. We are concerned with the health of consumers using these products, and are naturally interested in the laws regulating these products. In that regard, the following are recommended and detailed comments are attached:

1) Modify the present SPF In Vivo test.
2) Adopt an In Vitro UVA test
3) Do not require separate In Vivo UVA Testing
4) Do not require separate UVA labeling
5) Require products to be photostable
6) Do not cap SPF's
7) Extend time between Monograph notification and implementation

We appreciate the opportunity to make comments and hope these will be seriously reviewed.

An original and two copies are being supplied.

Sincerely,

Dennis L. Lott
Executive Director of Technical Affairs

78N-0038

C584

Ron Rice Beach Products

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I. TIMING

Separately on July 6 of this year Tanning Research Laboratories(TRLI) provided a letter discussing the monograph timing. We would like to reiterate the timing requests proposed in that letter. Basically the decision date must be pushed forward or the implementation date delayed. Not to belabor the points made in the earlier writing, it is imperative that the time between the final notice and the implementation be expanded. Two years is a reasonable time to respond. A June or July date is recommended for both dates since the shipping season is practically over at that time and manufacturing for the next season just beginning.

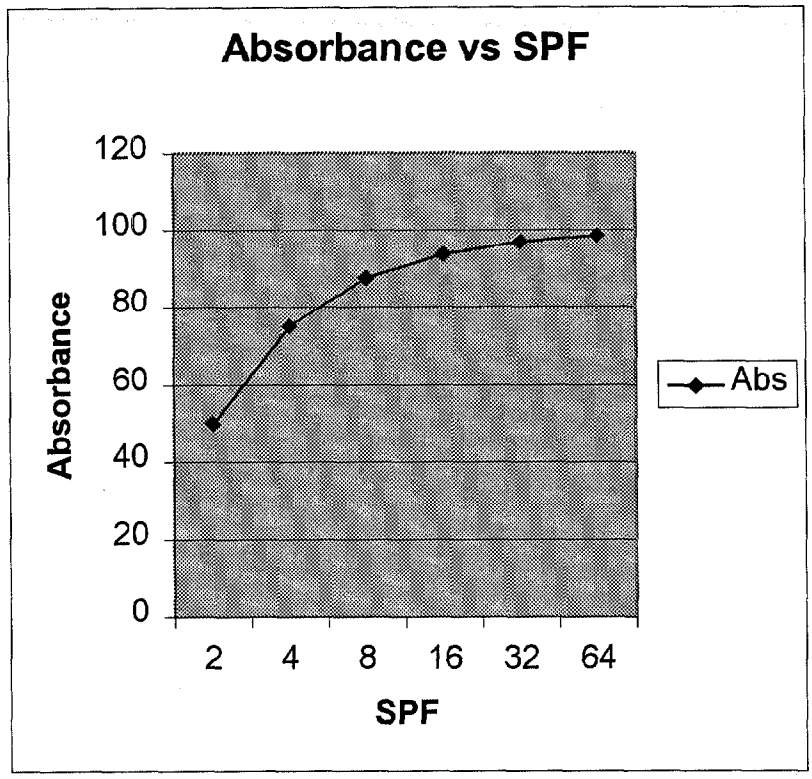
II. SPF Cap

The next major point TRLI would like to make concerns the cap of SPF's at 30. Previous comments from others have discussed in detail the need to protect for 50 or more MED's. We see no advantage to the consumer in capping the SPF at 30(30 +). In fact having a 30 + category for anything over 30 rather than allowing the actual tested SPF to be labeled will ultimately result in less protective products than are available today. Sunscreens are expensive, and we expect some manufacturers to ultimately use the minimum quantity necessary to produce a SPF over 30 if the cap remains. When evaluating the need for higher SPF's two main points come to mind:

A. Absorbance Change vs. SPF

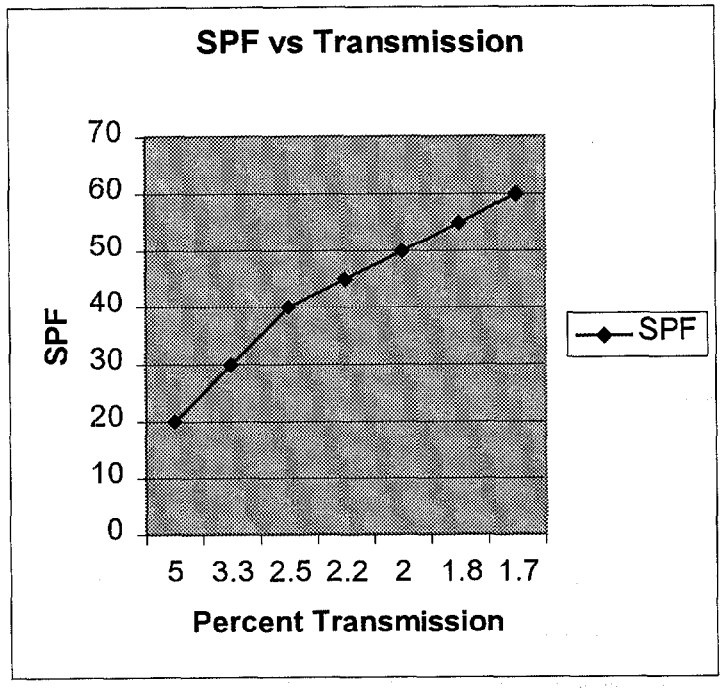
TRLI fully understands that absorption increases for high SPF's do not increase dramatically as the SPF climbs(in simplified terms an SPF 30 absorbs 96.7% while an SPF 50 absorbs 98%). This is graphically shown in Figure 1.

Figure 1



However, looking at it another way, the SPF 30 allows 3.3% of the sun's rays to penetrate while the SPF 50 only allows 2%. This means that 65% more sunlight penetrated with the SPF 30 than the SPF 50 as illustrated in Figure 2.

Figure 2



This is significant, but is even more significant when it is realized that in real life situations the user does not use the recommended quantity of product. We have never seen a study that indicates the consumer utilizes adequate product.[1] Numerous studies as the one cited here indicate the SPF is dependent on the quantity of sunscreen used.[2] Tanning Research Laboratories tested three different products at the accepted dosage level and at ½ of the dosage level, 2mg/cm^2 and 1mg/cm^2 respectively(Appendix 1). Surprisingly, the data appeared to be somewhat linear with the ½ dosage yielding approximately ½ of the SPF. The

data is summarized as follows:

Table 1

	SPF(Mean)	
	2mg/cm2	1mg/cm2
Formula 160-4	49.04(n=11, σ=9.23)	22.5(n=8, σ=2.6)
Formula 162-15	33.3(n=11, σ=4.9)	13.7(n=9, σ=2.5)
Formula 162-17	18.7(n=11, σ=3.2)	8.7(n=8, σ=1.5)

If the user only uses ½ of the tested amount, and this results in only ½ of the SPF, then the SPF 30 and SPF 50 example given above actually becomes an SPF 15 and SPF 25. Clearly, there is a high number of people that need this much protection, and unless habits can be changed, resulting in more sunscreen usage, higher SPF's are needed.

The caveat for having high SPF's is the inability to distinguish significant differences in the present in vivo test. This is discussed fully in another section. But the need should not be confused with the method limitations. We cannot change the need. We can improve the test method.

B. SPF Terminology

The SPF terminology usage is wrong. It is frequently implied or even stated by professionals that an SPF means the amount of protection provided by a product over and above the individual's normal protection. The person describing an SPF example usually says something like this: "if you can stay in the sun for 10 minutes normally, an SPF 10 will allow you to stay 10 times longer or 100 minutes in the sun". This terminology is inappropriate! The present endpoint of an SPF test for both the protected and unprotected skin is a dangerous condition(sunburn). If users sunburn in 10 minutes without protection, SPF 10 usage does not mean they should stay in the sun for 100 minutes. They will be

burned at 100 minutes. Unfortunately, it appears that the sun worshipper stays out in the sun until burned regardless of the SPF. This was suggested by a double blind study by Autier.[1]

Despite the previous discussion, this argument is not being promulgated to scrap the SPF system. It is believed that after years of marketing products with this numbering system, the users do recognize that the higher the number, the more protective the product. To jeopardize this now would be foolhardy. But, considering the two points made above, it appears that the only logical ways to more fully protect the consumer are 1)education of the dangers and more sun avoidance at peak sun times, and 2) provide ever more protective products that when used at even ½ of the dosage have a good chance of protecting users. Since, the public's desire for sun worship does not appear to be waning, it is probably safe to say that item 1 in itself will not be an adequate safeguard, although a warning on high SPF suncare packaging concerning excessive sunbathing dangers could help. This leaves more highly protective products as the only reasonable answer. Products should be available that are strong enough to protect all day even when used at ½ the dosage. But regardless of effectiveness, if the label does not communicate a measurable degree of protection because of the 30+ limitation, this will not be an effective safety measure. The consumer will not be allowed to recognize the safer product because of labeling restrictions.

There is perhaps one other change that would help the problem. As alluded to before, the the amount of test product applied could be halved. This would effectively lower all SPF's. TRLI is not recommending this action. It is unknown the problems that would be caused by changing the test quantity. It is conceivable that $1 mg/cm^2$ is not adequate for full coverage with some product forms. Given the problems with high SPF testing discussed further in this writing, it would need far more than the limited studies performed by Tanning Research Laboratories(Appendix 1).

III. TESTING OF HIGH SPF PRODUCTS

The agency has expressed concern about the variability of testing high SPF products. This concern is a valid one. There are significant variations. Originally the SPF test measured products with SPFs in the 2 – 8 range. We believe the test was and still is adequate for low SPFs. As discussed later in this writing high SPF testing is more problematic.

Before we discuss the cause of the variables, it may be necessary to review the test itself. What is the SPF test measuring? The test is very simply a measure of a sunscreen's ability to absorb light in the 290 to 400 nanometer(nm) range. The light source energy is divided by the energy that is transmitted through the sunscreen media, resulting in a ratio called Sun Protective Factor(SPF). This is similar to the test an analytical chemist would perform to analyze sunscreens or sunscreen containing products. The difference in the amount of light transmitted through a sunscreen solution in relation to the source light is compared to determine the amount of sunscreen material. Based on known validation data, it can be seen that absorption vs. concentration is very linear. The only exceptions might be extremely high and low quantities. Both the analytical method and the SPF method accuracies are dependent on the skills of the analyst/clinician to weigh, pipette, etc. Unfortunately, the SPF test has other variables that can also cause huge variations in high SPF testing and will be discussed later.

The only other real difference in the tests has to do with the method of light detection. Both have a light source, an adsorption media(sunscreen solution or film), and a light detector. The analytical chemist has a sophisticated piece of analytical machinery that is used to detect the light. The SPF Clinician has a human subject(no two the same) as the detector. Further the "human detector" has to measure light across a wave band of 290 nm to 400 nm whereas the chemist's machine is only using one wavelength for analysis purposes.

We are satisfied if a group of analytical chemist's can obtain results within ± 2 %. It certainly is not reasonable to expect the SPF Clinician to obtain better results. Unfortunately, the SPF test has other variables that can also cause large variations in high SPF testing. This important point will be graphically discussed later indicating the difficulties in accurately predicting high SPF's.

The differences in variability within the same lab is probably less significant when compared to the variability between different labs as shown in COLIPA "ring" tests[3], but still significant. Lab variability is believed to be primarily the result of five factors; 1) variation in solar simulators, 2) variation in product application, 3) variation in interpretation of MED's, 4) product migration outside the test site, and 5) test subject differences.

A. Variation in solar simulators

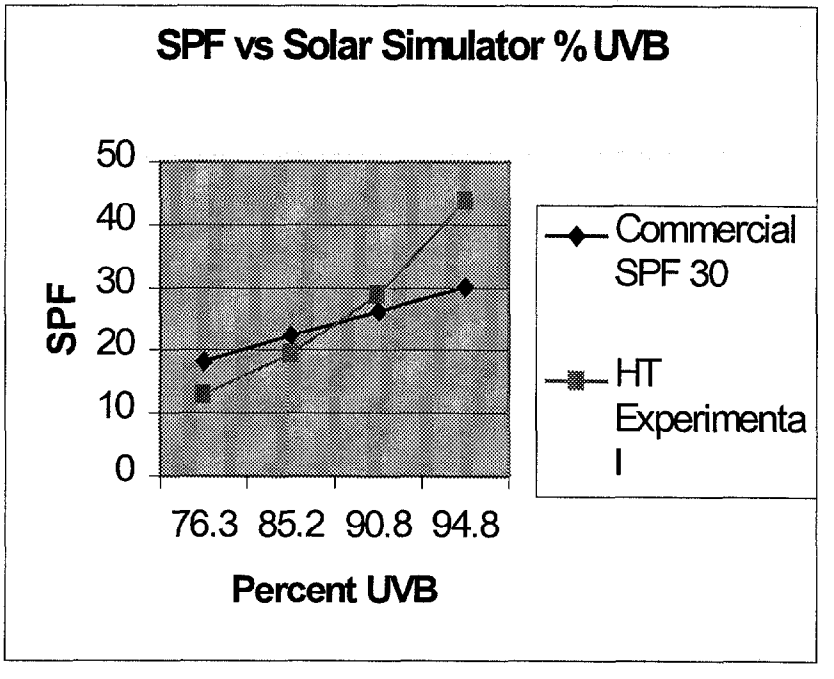
The agency has asked for comments concerning the use of COLIPA specifications for solar simulator standards. The COLIPA specifications for the amount of energy at various wavelengths, expressed as a percentage of the total Erythemal Effectiveness(RCEE)[3] is summarized below:

Table 2

Wavelength	% Energy Allowed
<290nm	<1.0%
290 –310	46 – 67%
290 – 320	80 –91%
290 – 330	86.5 – 95.0%
290 – 340	90.5 – 97.0%
290 – 350	93.5 – 99.0%

SPF tests performed near the minimum and maximum specifications above can cause SPF variation of 100% or higher. The variance is due to the difference in the light source spectra in conjunction with the formulation's absorption spectra. The following graph, Figure 3, depicts SPF's that can theoretically be obtained from the same formulation with varying solar spectras. These experimental results were obtained by performing in vitro scans on the product, Appendix II. This data was then expressed as transmission data. Using the transmission data at 5 degree increments the amount of energy at each wavelength increment was multiplied by the erythemial factor at that wavelength. The results were summed for wavelengths from 290 to 400. The energy sums needed to obtain an MED for protected and unprotected were compared to predict the SPF. This method or a slight variation thereof has been described by Sayre, et,al.[4]

Figure 3



The COLIPA document states that the typical SPF 15 European product could give a maximum error of 3 SPF units based on the Solar Simulator specifications. Additionally note the draft paper in Appendix 3 submitted for publication by

Stanfill, Sayre, and Lott that shows the difference in SPFs of the COLIPA p2 and p3 standard sunscreens This study was actually performed on the same subjects in the same lab. The different solar simulator caused statistically significant differences in the SPF.

B. Variation in product application

This is a problem that cannot be quantified in this writing, but theoretically is a source of huge variability. Several factors can have significant bearing on the results, including accuracy of measuring the product, accuracy of "staying" in the designated test site when applying, and how the product is "rubbed-in". We have no inter lab data but have "heard" of various labs using finger cots(as the monograph states), finger cots pre-saturated in product, gloves pre-saturated in product, and glass rods to smooth out the product. We have done limited studies showing that approximately .01gm of the 0.1gm/50 cm^2 remains on the finger cot after rubbing. This is helpful knowledge, but must be pursued further. For example, some high SPF products have as much as a 50% oil(non volatile) phase. Low SPF emulsions might only have a 10% non volatile oil phase, and oil products would probably have very little volatiles. While spreading the product in an extremely thin layer evaporation of volatiles occurs, and it is not reasonable to think that the product remaining on the finger cot is uniform. More than likely it is a higher percentage of the non volatile portion of the product. This should be high in sunscreen concentration. The extent of these variables has not been fully evaluated.

C. MED Interpretation

The agency tried to remove some of the uncertainty in scoring MED's in the 1993 proposed Tentative Final Monograph by proposing that a MED be the first detectable erythema with clearly defined borders rather than the first detectable erythema in the 1978 monograph. The agency also asked that there be intensity greater than the initial MED. As far as detection is concerned, this sounds straightforward, but in practice regardless of how severe the erythema, there is significant uncertainty in grading MED's. It appears that the test subjects are completely uncooperative in having smooth easy to read skin without blemishes, wrinkles, etc. Also, due to the varying amounts of UVB and UVA in solar simulator spectras, and the difference in skin types and their susceptibility to tanning, it is suspected that some MED's are actually tanning spots. There have been published reports that a "sunburn" produced by UVB and UVA are different in color and intensity.[5] If this is the case, it would have to be difficult to accurately grade an unprotected MED produced by a high UVB light source as compared to the protected MED that might be obtained after most of the UVB has been filtered.

D. Product Migration

This is a problem that may be significant for test purposes, but not in actual consumer usage. Independent test labs perform tests measuring the degree of product spreading or migration. The product is said to be "non migrating" if the test circle radius of material has not increased over 10% in 15 minutes. Simple geometry shows that the circle area will expand exponentially as the circle radius increases. A 10% circle radius increase means the product would occupy a 21% larger area after just 15 minutes. Obviously, if the product is not in the test site area it cannot contribute to the tested SPF, and the SPF will be understated. This probably has little significance except for "passing the SPF test". In most cases it is probably advantageous for a formulation to "spread" quickly to keep the user from missing spots when applying. But it is obvious that if a large portion of the product is outside the test site area in the monograph required minimum of 15

minutes between product application and exposure, the SPF is going to be understated and so variable to be unreliable.

E. Test Subject Differences

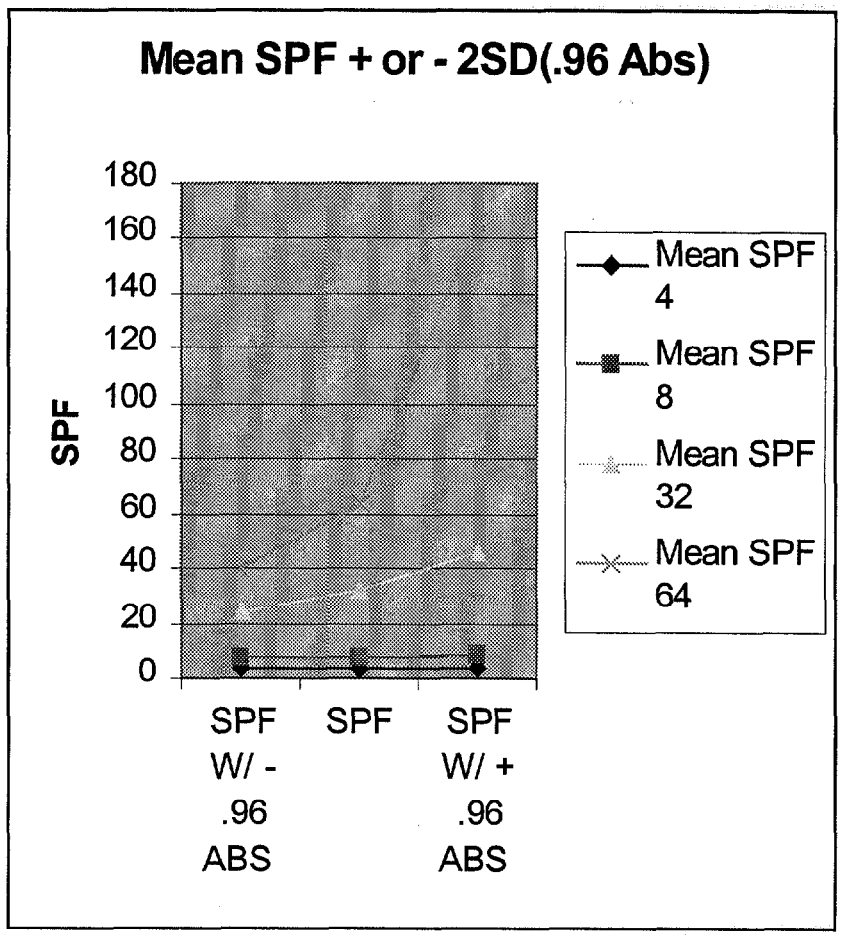
A fifth factor would be a source of both intra and inter lab variability and that is the differences in test subjects. This could either be the result of different test subjects or the same test subject tested at different seasons. This difference appears to be significant. Appendix IV shows the results of a TRLI study comparing 12 months of 8% Homosalate Standard sunscreen SPF results on the same subjects. Twenty five subjects were found to have been tested at least 6 times over a 12 month period. Note that this data comes from the same lab, same solar simulators, same lab personnel and same test subjects, thus effectively reducing the number of variables. The data analysis revealed that there was a statistically significant decrease in SPF for the three month period of July, August, and September. Summarizing, the mean SPF for the 12 month period was 4.9. The mean SPF for July, August, and September was 4.52 for a P-value of .00016. Many investigators would have predicted that any sun exposure, even through clothing, will change the skin's response to further exposure. More than likely the test subjects have received some exposure in the spring and early summer months making them less sensitive to further exposure.

What is the significance of all the variables discussed above? Simply put, the present SPF test is more than adequate for testing low SPF's(<15) because the difference in absorbances at those levels are detectable. However, as attempts are made to test higher SPF's the many test variables discussed above quickly become larger than the differences in absorbances that must be detected. This is mathematically illustrated further in this writing.

In reviewing the variance of the TRLI study in Appendix VI, which we believe is probably one of the more closely controlled studies ever attempted, what are the SPF detection limits? If the SPF data is converted to absorbance so that the effect at any SPF

can be calculated it is seen that $1\sigma \cong 2.19$ absorbance units. For a 20 subject test within a 95% Confidence Limit, the standard error would be expected to change by approximately $z(2.19)/\sqrt{20}$ or $(1.96 \times 2.19)/\sqrt{20} = .96$ absorbance. For an approximate ± 2 RSD($\pm .96$ fluctuation in absorbance) to obtain a 95% confidence limit the SPF would have approximate ranges as indicated in Figure 4.

Figure 4



The data shows that if a product has a mean SPF of 32 the next lower value that can be detected with a 95% confidence is approximately 24. Likewise the next higher value is approximately 46. Obviously, as the SPF increases the spread becomes larger, with the upper 95% interval approaching infinity.

It is clear that given the limits of the test, the tested SPF is a good approximation at SPF's less than 15, but at higher SPF's the numbers that would be found within a 95% confidence range are too large to contemplate testing.

IV. NECESSARY TEST SUBJECTS FOR 95% CONFIDENCE

Given the projected range in SPF's shown in III, to obtain a 95% confidence limit, how many subjects will be needed to accurately predict high SPF's? If the product being tested is an SPF 50, the clinician is attempting to measure differences in product absorbances of 98% vs. 97%, vs. 99%, etc. The endpoint to measure these differences is a biological endpoint on different people with different skin types, etc. The SPF difference between the product absorbing 98%, 97%, and 99% are SPF 50, 33, and 100 respectively. As discussed in III, analytical chemist results within $\pm$2% would be acceptable analytical validation criteria between different analysts. If we are satisfied with results from a skilled analytical chemist to obtain results of varying absorbances of $\pm$2%, how can we expect a clinician to obtain more precise results based on biological responses that would be reflective of accuracy's that are far greater. Granted that by using a 20 subject panel the average SPF the clinician obtains has a better chance of approximating the actual value, but it is probably impossible for minor differences in absorption to be detected.

What are the limits that we want to achieve? The proposed monograph prescribed increasing UV doses for high SPF products as follows:

.76x, .87x .93x, x(Target SPF), 1.07x, 1.15x, 1.32x

If we want to obtain the ability to detect $\pm$ 7%(based on testing intervals around the target suggested in the monograph for high SPF products), how many subjects are needed? The number of samples(subjects) needed for an SPF 50 could be estimated as by converting the expected SPF to absorbance:

SPF 46.5(-7% of 50 Target) = Abs. of 97.85%

SPF 50 = Abs. of 98%

SPF 53.5(+7% of 50 Target) = Abs. 98.13%

This would average to an absorbance of 98 $\pm$.14. As can be seen further in this discussion evaluating the number of subjects needed for a 95% confidence interval, there

is no chance in detecting a ± 7% difference. Therefore we will only evaluate the number of subjects needed to detect 25% dosage increments. The next parameter that needs defining for our estimation is the absorbance standard deviation(σ) to be used. This is obviously an estimate. If we use the TRLI data, Appendix IV, the standard deviation would be about 2.2. Therefore, we are arbitrarily, but not unrealistically, picking a standard deviation of 2 for our calculations.

To determine the number of subjects(n) for the desired confidence interval(c) with a standard deviation(σ) the following calculation will be used:

$$n = ((\sigma 1.96)/c)^2$$

Then the values of n can be calculated and are shown below in Table 3:

Table 3

Target SPF	SPF + 25%	25 % Abs Confidence Interval (c)	n
10	12.5	2	4
15	18.75	1.33	9
20	25	1	15
25	31.25	0.8	24
30	37.5	0.67	35
50	62.5	0.4	96
100	125	0.2	384

The 25% confidence interval is obtained by converting the SPF's to absorbance and subtracting. The formula is as follows:

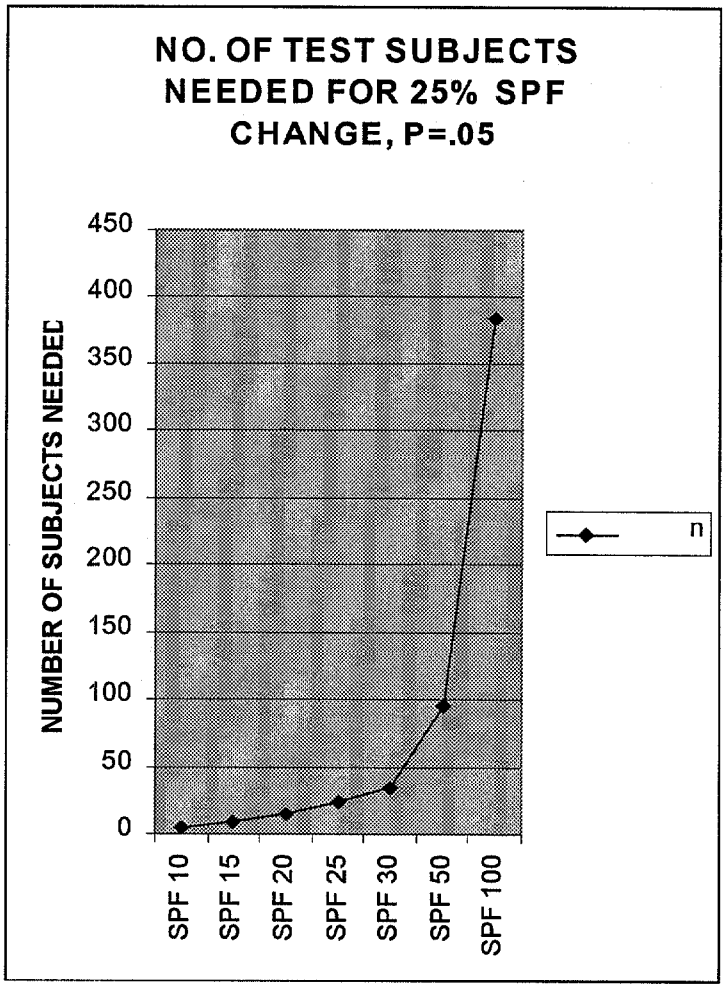
Confidence interval(c) = (100-100/SPF+25%) – (100-100/SPF).

Sample calculation for Target SPF 50:

$$n = ((2 \times 1.96)/.4)^2 = 96$$

Thus it can be seen that the SPF test with 20 subjects is valid for up to SPF 20, but as SPFs go higher the number of subjects needed climb exponentially. This data is graphically shown in Figure 5.

Figure 5



As can be seen, to accurately predict a high SPF the number of subjects needed still quickly becomes an unworkable number. Clearly the system for predicting high SPF's must be refined.

V. UVA

The agency is concerned that SPF alone is not an adequate measure of UV protection. The concern has been expressed that by protecting a user from sunburn, we are allowing them to stay in the sun longer and receive higher quantities of damaging UVA. This logic has been espoused by many and has led to an ongoing debate in the US that has led to an implementation delay of the US final monograph. There are several issues being debated:

1) Is UVA dangerous?
2) How are UVA protection factors to be measured?
3) How are UVA protection factors to be labeled?
4) Photostability?

A. UVA Dangers

The first question obviously determines the need to answer the others. Few will argue the point that the portion of the UVA that cause erythema is dangerous. The present SPF system provides protection for short wavelength UVA(UVA II, 320 –340)and probably higher. This has been shown earlier in this writing. Therefore, the need for UVA protection can only be referring to longer wavelength UVA(UVA I, 340 - 400). Recently many papers and articles have been printed stating the dangers of UVA. One argument is that by protecting from UVB, higher doses of UVA are realized, and this causes Melanoma. This has not been proven. There is not a consensus on the danger of UVA I. There are studies that seem to implicate UVA as being a carcinogen, and many that seem to indicate UVA to be benign[6,7]. The danger of UVA has not been quantified, and in fact may never be fully quantified because there may not be exact answers. It is not reasonable to expect that all skin types are susceptible to the same harm when subject to the same radiation spectra. In fact it is almost guaranteed that this is not the case. It is not an accident that lighter skin people habitat latitudes further

away from the equator and vice versa. Human skin types are directly related to their historical ancestor latitudes. In fact the major problems appear to be when after years of adaptation to a particular climate, a major latitude move causes problems. Examples would be people from the UK populating Australia, and the incredible increase in skin cancer rates of Australians compared to the English. A reverse example is seen when other cancer incidences of darker skin people are compared when they have migrated away from the equator. It is postulated that this lack of sun causes many more health related problems and deaths than over exposure[8,9,10].

Recent studies with the South American Possum appear to emphatically show that Melanoma is caused by UVB, not UVA[11,12]. Contrary to this a recent study shows that Melanoma in the United States appears to be just as prevalent in higher latitudes than lower latitudes[13]. This could lead to the conclusion that since there is relatively more UVB at lower US latitudes and relatively more UVA at higher latitudes that UVA is the Melanoma culprit. Interestingly, an evaluation of TRLI sunburn complaint data, shows that almost all sunburn complaints have the same pattern:

a. They are in spring or early summer – 48% were at July 4th
b. Most appear to be related to non routine activity, vacation, beach, pool, etc. – 58% were at a beach setting(not all salt water beach)
c. The average latitude gradient from where the complainants live as compared to where the sunburn occurred when the vacation was out of state was is about 11 degrees closer to the equator.
d. 68% of the complainants lived north of latitude 35, which roughly splits the U.S. Based on the population above and below this would only have been expected to be 62%
e. A full 90% of the complaints involve either **beach or July 4th.**

A typical complaint scenario could be summarized: the people live in Philadelphia, have not been in the sun throughout the winter, go to Daytona Beach on July 4th, go to the beach all day, typically use ½ or less of the needed quantity of sunscreen, and predictability burn themselves with a huge dose of

solar radiation that is high in UVB. When this is coupled with the fact, that several studies have shown that the at most risk people are not the chronically exposed outdoor worker but the casual "sunbather/beach goer"[14,15], it appears logical that high north latitude melanoma rates may still be caused by the massive doses of UVB obtained while vacationing closer to the equator. Although our data may not be predictable nationally, it is indeed strange that a higher percentage of people residing in north U.S. apparently receive an abnormally high amount of sunburn.

The previous arguments notwithstanding, it should be emphatically stated that Tanning Research Laboratories is not arguing that UVA protection is not important. What is being said is that more cause and effect studies need to be done before a policy is established that might be detrimental. TRLI does think that there is misinformation being disseminated essentially stating that "UVA is more harmful", "only buy sunscreens that contain UVA protection", and even that "sunscreens do more harm than good" that deters important sun preventive health measures. We do not perceive that UVA protection in high SPF products will cause harm unless there is a reduction in overall UVB protection. Therefore it appears logical that in adding protection the net effect will probably be positive as long as in doing so we do not make it more difficult for the consumer to understand or use. Referring back to the many studies that show that people do not use adequate quantities of sunscreen, and the fact that several studies show that intermittent sun worshippers are the greatest at risk , we should take precautions in not making products that are difficult to understand or that are more costly. It would seem logical that either would not lead to more usage and really defeat the whole purpose.

B. UVA Protective Factor Measurement

How are UVA factors to be measured? This is obviously a hotly debated item. In discussing this we first should remember that SPF is sometimes erroneously referred to as a measure of UVB. This is wrong! The endpoint for a SPF test is sunburn including that from UVB and UVA exposure. Referring back to the

discussion on high SPF's, it is easily seen that sunburn protection cannot be obtained without substantial UVA protection. This has been stated by many professionals with this writer seeing statements that SPF's no higher than 8, 15, etc. can be obtained without UVA protection. Actually this is highly dependent on the spectral source. The following graph, Figure 7, shows the SPF dependence on UVA protection. If the range of spectra based on the COLIPA standards are used, and a product that would provide an SPF 50 in the UVB range has 0 protection in the UVA range, the maximum SPF's that could be obtained would range from about 6 to about 12. If the protection is SPF 50 up to 360 nm and 0 from 360 to 400, the maximum SPF's that could be obtained would range from about 27 to 36 depending on the solar spectra. **Thus, it is impossible to get extremely high SPF's without UVA protection.** The SPF system clearly also measures some degree of UVA protection.

Figure 7

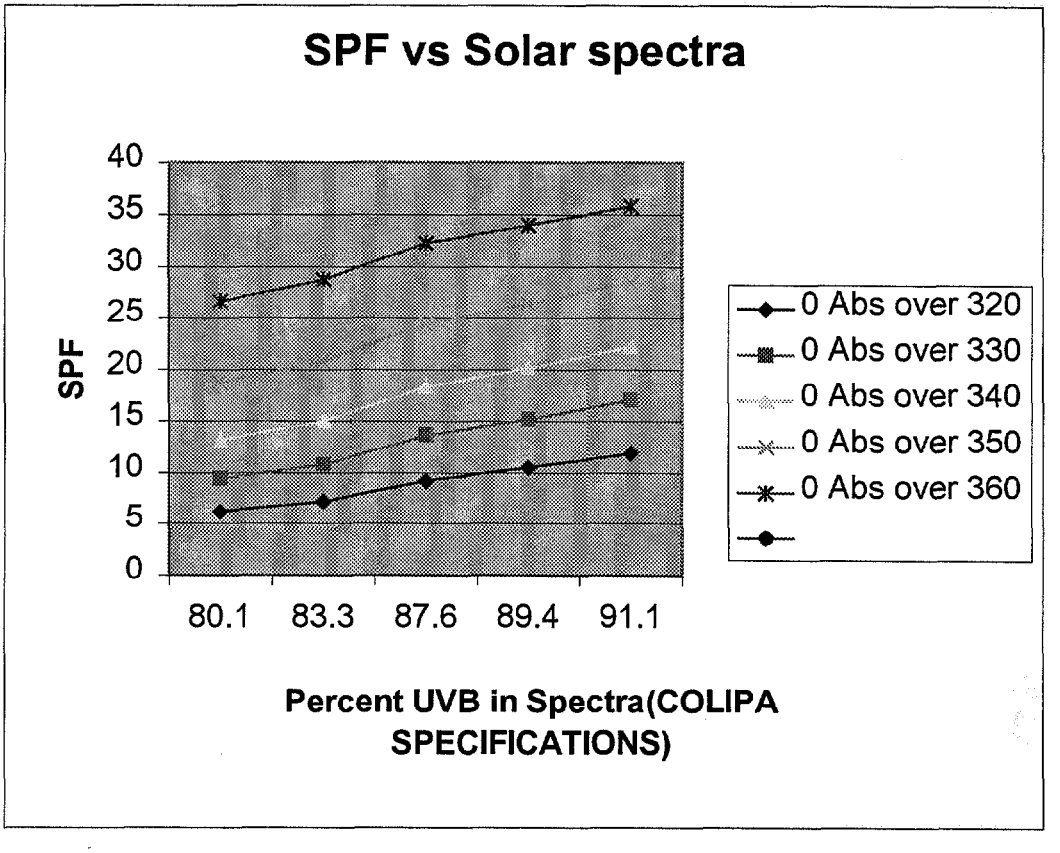


Figure 7 indicates the range of SPFs that will be obtained without absorbance beyond various UVA wavelengths. The X axis is based on the acceptable limits of UVB in the COLIPA solar spectra.

Getting further into the debate of UVA methods it appears that there are three pimary methods or some form thereof that are being debated:

1) Persistent pigment Darkening(PPD)
2) Initial Pigment darkening(IPD)
3) Critical Wavelength

The PPD and IPD are in vivo methods. These methods are disturbing. The problems associated with these methods were eloquently discussed by Brian Diffey at the American Association of Dermatology UVA Consensus Conference in Washington DC, Feb. 4, 2000. One very important factor raised by Diffey was the unusual radiation doses applied to human test subjects. It appears strange that these tests do not work on Type I skin, the skin type that would benefit the most from protection.[16] Although we do not have studies, it would appear very probable that the UVA "Protection Factor" obtained with these in vivo tests would be subject to all the detection limitations as those discussed for UVB in vivo testing.

The Critical Wavelength method uses an In Vitro scan to show the absorbance over a wide area. The wavelength cut off that is necessary to have 90% of the absorbance under the area of the curve is the "critical wavelength". Obviously, the higher this wavelength , the more the protection stretches into the higher wavelength areas of UVA. This method appears to better quantify the product absorbance spectra, is easily performed, and does not pose a human test subject risk.

C. UVA Labeling

This is tricky. The needs of the consumer should be foremost in this consideration. Since it is believed that SPF is somewhat understood, we do not believe that this method of labeling should be scrapped. The real question then becomes how do we add language that communicates the UVA level of protection without further confusion. The most logical way may be to make UVA protection transparent. In other words, do not change the labeling(SPF is the only criteria), but require that all products contain a certain amount of UVA protection as a minimum.

D. Photostability

Any regulation concerning UVA protection, must also address photostability. The best chemical sunscreen available in the US to aid in obtaining broad spectrum activity is Parsol 1789™(avobenzone). Many sunscreen combinations with avobenzone are believed not photostable.[17,18,19] Regardless of how the protection is to be measured and how it is to be labeled it seems logical that the product should maintain most of the "broad spectrum" and SPF activity throughout the expected consumer time in the sun. To our knowledge there are no universally accepted ways to measure this activity, but they all involve measuring the product protective qualities across the full spectra, stressing the product by subjecting to several MED's, re-measuring the activity across the spectra, and then comparing the activity before and after stressing. TRLI is of the opinion that both the SPF and the "UVA" protection should maintain a minimum level of activity after stressing. This has been a big issue in Europe for some time, and with the impending regulation concerning UVA in the US, is obviously becoming a bigger issue here also.

VI. RECOMMENDATIONS

A. Modify the SPF In Vivo Test

The present in vivo test should be modified. The present test is not adequate for the following reasons:

1) The difference in solar simulators can provide as much as a 200% variation in results depending on the formulation.
2) The variables in testing high SPF products are too great to obtain a 95% confidence level without testing an impossible number of subjects.
3) The test requires a potentially dangerous condition, sunburn, to be induced on test subjects.

The test is probably valid for lower SPF's. In fact extremely low SPF's probably do not even require the 20 subject panels. However, high SPF's cannot be predicted without using unworkably high number of test subjects. A pass/fail test in possible conjunction with the in vitro method discussed below will produce a more accurate and consistent results. The pass/fail test would show that subjects have no reaction to a quantity of energy equivalent to the expected SPF. An example as to how this could work is as follows:

1) Using existing data available from solar simulator calibrations, the average MED can be predicted for each skin type.
2) A test subject is carefully screened for skin type.
3) The subject is given a first day range of energy that does not exceed the expected MED. The goal is to obtain a very, very faint MED.
4) Depending on the information gained in item 3, the subject is given the amount of exposure corresponding to the expected minimum SPF on more than 1(perhaps 5) sub test sites. If the subject does not show

erythemia, then the product would be judged to "pass" the test for the expected SPF. Based on the number of sub test sites(n) the probability that a product is over or equal to the SPF in question can be predicted. A "pass" would result in there being more than a 95% probability. The goal of this test would be to reduce the test to a Binomial experiment, i.e. only one of 2 events can happen. In this case the two events are pass or fail. For example; if we have a formula that is believed to be about SPF 30, and we dose subjects at only the SPF 30 level, the results would be expected to either fail, produce an MED at the exposure sites, or pass, produce no detectable MED at the exposure sites, meaning the product is above an SPF 30. These are the only two events that can happen, thus binomial probabilities can be used for evaluation. If each of 5 subjects were given 4 separate doses corresponding to SPF 30 within a test site, and then judged if any recognizable MED occurred, the following predictions based on standard binomial probability tables could be made:

a. If 6 or more of the 20 sub test sites had perceptible MEDs the product failed. There would be less than a 95% probability the SPF was more than 30.
b. If < 6 had perceptible MEDs the product passed, i.e. there was more than a 95% probability the SPF was more than 30.
c. If after reading the first two subjects, 8 subsites, all passed, then the product would pass. The probability of this happening would be $(1/2)^8$ or 1/256 unless the product is over a SPF 30. In fact if after 5 sub site reads there were no failures, then the probability would be $(1/2)^5$ or 1/32 probability the product is not an SPF 30 or below. Summarizing the probabilities would be as shown in Table 4:

Table 4

No. of Subjects	Max # of failures	p
1 subject(n=4)	0	.0625*
2 subjects(n=8)	2	.0352
3 subjects(n=12)	3	.0200
4 subjects(n=16)	5	.0383
5 subjects(N=20)	5	.0207
*n is insufficient to make a 95%(.05) prediction		

The primary goal of the above proposed method is to reduce(hopefully eliminate) the amount of potentially dangerous erythemia presently induced on test subjects, and still maintain an in vivo test. Based on previous data and discussions in this document, we believe that the present in vivo test will not distinguish differences between SPF's of 40 and 45, 45 and 50, etc. Perhaps at this time three levels of high SPF sunscreens, SPF 30, 50, and even 100 could be tested and distinguished, by the pass/fail criteria.

B. Adopt an In Vitro UVA Test

Given previous discussions concerning the impossibility of obtaining high SPFs without having UVA protection, an in vitro test may not be necessary to insure broad spectrum activity. However, the test could show how broad the absorption spectra really is, and some form of in vitro will probably be necessary to check photostability. The test is certainly not dangerous and more meaningful than proposed in vivo UVA tests.

C. Do Not Require Separate In Vivo UVA Testing

Given the in vivo SPF test will necessitate UVA protection to obtain high SPF's, separate tests will not be necessary. Also, in vivo UVA testing would have all the problems that in vivo UVB testing exhibits.

D. No UVA Labeling Requirements

Given the above suggested requirements that UVA be present to obtain SPF it would be redundant and confusing to require additional labeling.

E. Photostability Should Be Required

All products should maintain a certain percentage of the protective properties throughout a use cycle. There needs to be a standard developed for testing photostability that is easy and reliable.

F. No SPF Cap

We see no advantage to capping SPF. The consumer needs the highest level of protection available. There is no logical reason to restrict this except for the testing inabilities. There is no need for every possible SPF number product to be available, although we do think that the pass/fail test recommended will be able to distinguish SPF's exceeding any given value. Based on the above comments, we propose that SPF's be allowed as follows;

1) Any SPF up to 20(present test or preferably the safer proposed pass/fail test).
2) 25 for a SPF tested as a mean of 25 or higher on the proposed binomal pass/fail test.
3) 30 + for anything tested to "pass" the above proposed binomial SPF test

4) 50 + for anything tested to "pass" the above proposed SPF binomial test
5) 75 + for anything tested to "pass" the above proposed binomial SPF test
6) 100 + for anything tested to "pass" the above proposed binomial SPF test(today's technology may not accommodate a commercially acceptable SPF 100 product, but the need is still there).

G. Timing

As stated in a previous comment, industry must have time to react to a Final Monograph. A minimum of 2 years between final publication and implementation is appropriate. Final publication and implementation dates should be in the June/July time period.

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Appendix 1

RESEARCH & DEVELOPMENT

EVALUATION OF SUN PROTECTION PRODUCTS BY SPF DETERMINATION

Project no. : Special Test

Date : November 12, 1999

Sample no. : 160-4, 162-17, 162-15

Client : HT

SAMPLE DESCRIPTION:

Reference no.	Product W/ Label SPF
160-4	HT 45 SPF Plus Lotion
162-15	HT 30 SPF Plus Lotion
162-17	HT 15 SPF Plus Lotion

A special test was conduted during the test weeks beginning on November 1 and November 8, 1999 on three products FR# 160-4, 162-15, and 162-17. These products submitted as HT 45 SPF Plus Lotion, HT 30 SPF Plus Lotion, and HT 15 SPF Lotion had been previously tested during the weeks of June 28 and July 6, 1999. All products were tested under the guidelines set forth under the new Final Monograph, FDA, May 21, 1999 (Volume 64, Number 98), Rules and Regulations, page 27666-27693.

All products were tested under "static" conditions (without water immersion) during all test periods. Tables No. 1, 2, and 3 reflect the test results yielded during the initial testing conducted during the weeks of 6/28/99 and 07/06/99. Tables 4, 5, and 6 reflect the results yielded during a second test period in which the same products were tested using the same methods and guidelines with one exception. The products tested during the test period of 11/01/99 through 11/12/99 were tested using one-half the amount of product which is normally applied to the test area. 1 mg per cm2 was applied instead of the normal concentration of 2mg per cm2. This was done in order to test the effects of absorbancy and to determine the "threshold" at which concentrations of test material applied to the test area would have a significant effect on the expected SPF value. (I.e. would 1/2 of the normal amount of test material applied yield 50% of the normal expected SPF value or would these values be somewhat higher or lower.)

The results from both test periods are included in the following tables for comparison.

Table 1

Project No: HT #070699, HT #062899

Reference No: 160-4 (HT 45 SPF Lotion)

Subjects Tested: 11

Subject Name	Sex	Base M.E.D.	Skin Type	157-53 Std. (8% HOMO)	160-4 45 SPF (Static)
039-42-9017	F	8/6	II	6.25	60.19
063-40-5459	F	10/13	III	5.00	41.40
214-42-5585	F	6/8	II	5.00	36.00
358-64-2122	M	6/6	I	5.00	51.75
413-68-1373	F	8/8	II	4.40	59.40
261-72-0754	F	6/6	I	5.00	51.75
262-93-4052	M	8/8	II	6.24	59.40
219-62-1443	M	8/8	III	5.00	39.15
265-19-0042	M	8/8	II	5.00	41.85
267-74-6585	F	6/6	III	6.24	59.40
265-59-2268	F	8/8	II	4.40	39.15
AVERAGE: (X)				5.23	49.04
STD DEVIATION:				0.66	9.23
STD ERROR OF MEAN:				0.20	2.78
STD % ERROR OF MEAN:				3.80	5.67
A = ts / sq root n				0.44	6.20
X - A				4.79	42.84
LABEL SPF:				4.00	42.00

(Largest whole number < X-A)

t = t value from the "two-sided" student distribution table at probability level 0.05 with n-1 degrees freedom

Table 2

Project No: HT #070699, HT #062899

Reference No: 162-15 (HT 30 SPF Lotion)

Subjects Tested: 11

Subject Name	Sex	Base M.E.D.	Skin Type	157-53 Std. (8% HOMO)	162-15 30 SPF (Static)
039-42-9017	F	8/6	II	6.25	40.13
063-40-5459	F	10/13	III	5.00	31.68
214-42-5585	F	6/8	II	5.00	24.00
358-64-2122	M	6/6	I	5.00	39.60
413-68-1373	F	8/8	II	4.40	32.10
261-72-0754	F	6/6	I	5.00	34.50
262-93-4052	M	8/8	II	6.24	34.50
219-62-1443	M	8/8	III	5.00	30.00
265-19-0042	M	8/8	II	5.00	32.10
267-74-6585	F	6/6	III	6.24	39.60
265-59-2268	F	8/8	II	4.40	27.90
AVERAGE:				5.23	33.28
STD DEVIATION:				0.66	4.87
STD ERROR OF MEAN:				0.20	1.47
STD % ERROR OF MEAN:				3.80	4.41
A = ts / sq root n				0.44	3.27
X - A				4.79	30.01
LABEL SPF:				4.00	30.00

(Largest whole number < X-A)

t = t value from the "two-sided" student distribution table at probability level 0.05 with n-1 degrees freedom

Table 3

Project No: HT #070699, HT #062899

Reference No: 162-17 (HT 15 SPF Lotion)

Subjects Tested: 11

Subject Name	Sex	Base M.E.D.	Skin Type	157-53 Std. (8% HOMO)	162-17 15 SPF (Static)
039-42-9017	F	8/6	II	6.25	22.50
063-40-5459	F	10/13	III	5.00	17.28
214-42-5585	F	6/8	II	5.00	17.28
358-64-2122	M	6/6	I	5.00	21.60
413-68-1373	F	8/8	II	4.40	21.60
261-72-0754	F	6/6	I	5.00	21.60
262-93-4052	M	8/8	II	6.24	18.00
219-62-1443	M	8/8	III	5.00	16.35
265-19-0042	M	8/8	II	5.00	12.45
267-74-6585	F	6/6	III	6.24	21.60
265-59-2268	F	8/8	II	4.40	15.00
AVERAGE: (X)				5.23	18.66
STD DEVIATION:				0.66	3.17
STD ERROR OF MEAN:				0.20	0.96
STD % ERROR OF MEAN:				3.80	5.13
A = ts / sq root n				0.44	2.13
X - A				4.79	16.53
LABEL SPF:				4.00	16.00

(Largest whole number < X-A)

t = t value from the "two-sided" student distribution table at probability level 0.05 with n-1 degrees freedom

Table No. 4

Project No: HT #110899, HT #110199

Reference No: 160-4 (HT 45 Plus Lotion)

Subjects Tested: 9

Subject Name	Sex	Base M.E.D.	Skin Type	1/2 Normal Application 157-53 Std. (8% HOMO)	160-4 23 SPF Static
158-36-6961	F	15/15	III	4.40	TF
232-23-3506	F	10/10	III	5.00	23.49
380-64-2044	F	10/10	III	5.00	20.52
401-06-6906	F	10/10	II	5.00	17.48
261-72-0754	F	6/6	II	5.00	27.00
294-11-4679	M	8/8	II	5.00	23.00
263-41-1894	F	8/8	II	4.40	23.00
216-74-5519	F	8/8	II	4.00	24.32
342-52-0787	F	12/12	II	5.00	21.39
AVERAGE:				4.80	22.53
STD DEVIATION:				0.36	2.63
STD ERROR OF MEAN:				0.13	0.93
STD % ERROR OF MEAN:				2.66	4.13
A = ts / sq root n				0.29	2.10
X - A				4.51	20.42
LABEL SP (Largest whole number < X				4.00	21.00

t= t value from the "two sided" student distribution
table at probability level 0.05 with n-1 degrees freedom

NOTE: The amount of test product applied to each subject for this test was at one half of the normal amount (1 mg per cm2 instead of the normal 2mg per cm2). This was done to test the effect of absorbancy and to determine the "threshold" at which the concentrations of test material applied would effect expected SPF values.

Table No. 5

Project No: HT #110899, HT #110199

Reference No: 162-15 (HT 30 Plus Lotion)

Subjects Tested: 9

Subject Name	Sex	Base M.E.D.	Skin Type	1/2 Normal Application 157-53 Std. (8% HOMO)	1/2 Normal Application 162-15 18 SPF Static
232-23-3506	F	10/10	III	5.00	11.52
401-06-6906	F	10/10	II	5.00	10.35
380-64-2044	F	10/10	III	5.00	11.52
158-36-6961	F	15/15	III	4.40	13.65
261-72-0754	F	6/6	II	5.00	18.00
294-11-4679	M	8/8	II	5.00	15.00
263-41-1894	F	8/8	II	4.40	12.45
216-74-5519	F	8/8	II	4.00	17.48
342-52-0787	F	12/12	II	5.00	13.65
AVERAGE:				4.76	13.74
STD DEVIATION:				0.36	2.51
STD ERROR OF MEAN:				0.12	0.84
STD % ERROR OF MEAN:				2.54	6.09
A = ts / sq root n				0.27	1.89
X - A				4.48	11.84
LABEL SP (Largest whole number < X				4.00	11.00

t= t value from the "two sided" student distribution
table at probability level 0.05 with n-1 degrees freedom

NOTE: The amount of test product applied to each subject for this test was at one half of the normal amount (1 mg per cm2 instead of the normal 2mg per cm2). This was done to test the effect of absorbancy and to determine the "threshold" at which the concentrations of test material applied would effect expected SPF values.

Table No. 6

Project No: HT 110899, HT #110199

Reference No: 162-17 (HT 15 Plus Lotion)

Subjects Tested: 9

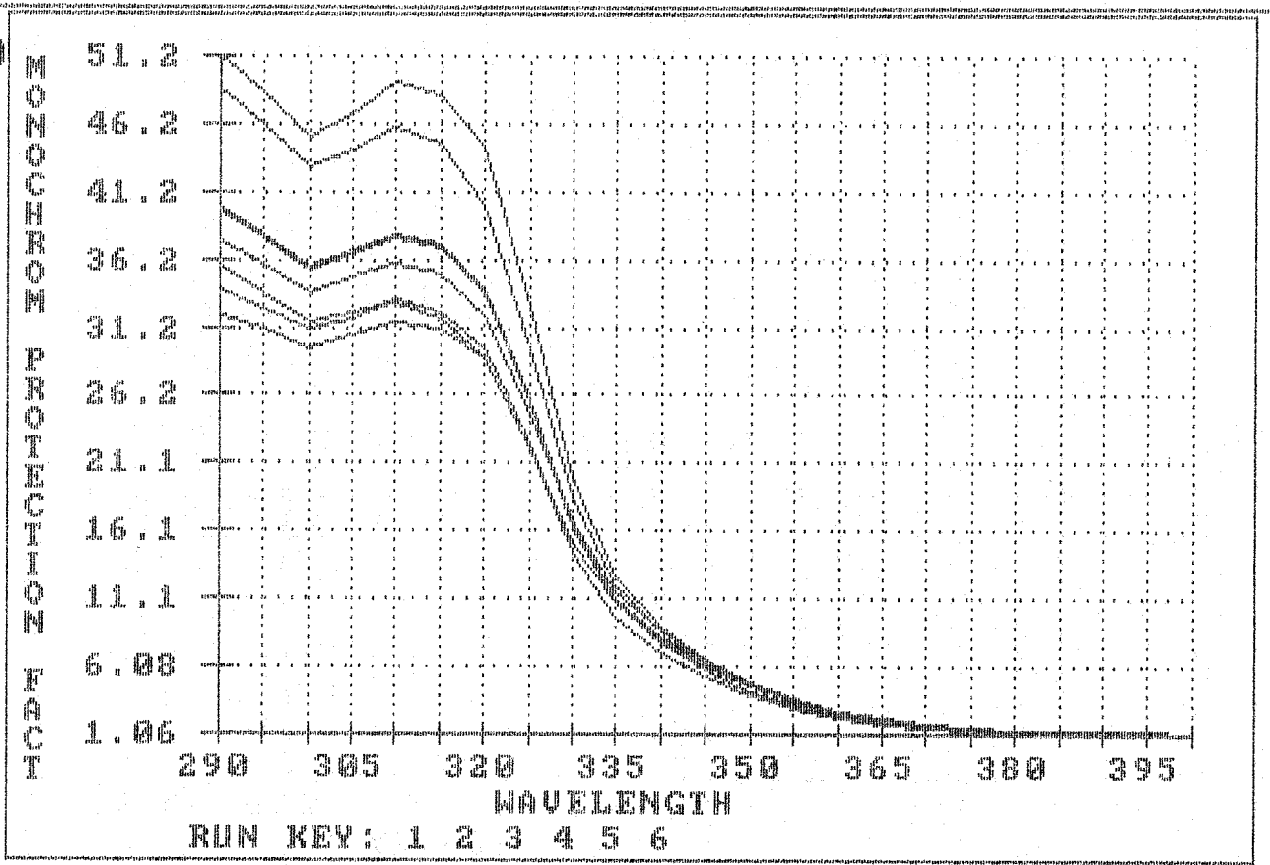
Subject Name	Sex	Base M.E.D.	Skin Type	1/2 Normal Application 157-53 Std. (8% HOMO)	1/2 Normal Application 162-17 8 SPF Static
401-06-6906	F	10/10	II	5.00	TF
232-23-3506	F	10/10	III	5.00	9.10
380-64-2044	F	10/10	III	5.00	8.30
158-36-6961	F	15/15	III	4.40	7.28
261-72-0754	F	6/6	II	5.00	12.00
294-11-4679	M	8/8	II	5.00	8.00
263-41-1894	F	8/8	II	4.40	9.60
216-74-5519	F	8/8	II	4.00	6.90
342-52-0787	F	12/12	II	5.00	8.00
AVERAGE:				4.76	8.65
STD DEVIATION:				0.36	1.51
STD ERROR OF MEAN:				0.13	0.53
STD % ERROR OF MEAN:				2.69	6.17
A = ts / sq root n				0.29	1.21
X - A				4.47	7.44
LABEL SP (Largest whole number < X				4.00	7.00

t= t value from the "two sided" student distribution
table at probability level 0.05 with n-1 degrees freedom

NOTE: The amount of test product applied to each subject for this test was at one half of the normal amount (1 mg per cm2 instead of the normal 2mg per cm2). This was done to test the effect of absorbancy and to determine the "threshold" at which the concentrations of test material applied would effect expected SPF values.

Appendix 2

Lambda	MPF	+/- SD
290	39.9	8.2
295	38.0	7.5
300	35.7	6.7
305	36.8	7.0
310	38.1	7.6
315	37.2	7.4
320	34.0	6.7
325	25.7	4.5
330	16.7	2.3
335	11.1	1.3
340	8.1	.9
345	6.1	.6
350	4.5	.5
355	3.3	.3
360	2.5	.2
365	2.0	.2
370	1.6	.1
375	1.4	.1
380	1.3	.1
385	1.2	.0
390	1.1	.0
395	1.1	.0
400	1.1	.0



Sample: Comm_spf30 Runs: 6 06/06/00 12:43:13
Thickness: 2.0 ul/cm2 Ref: Comm. SPF Operator: glenn
File: COMMKD30.SPF

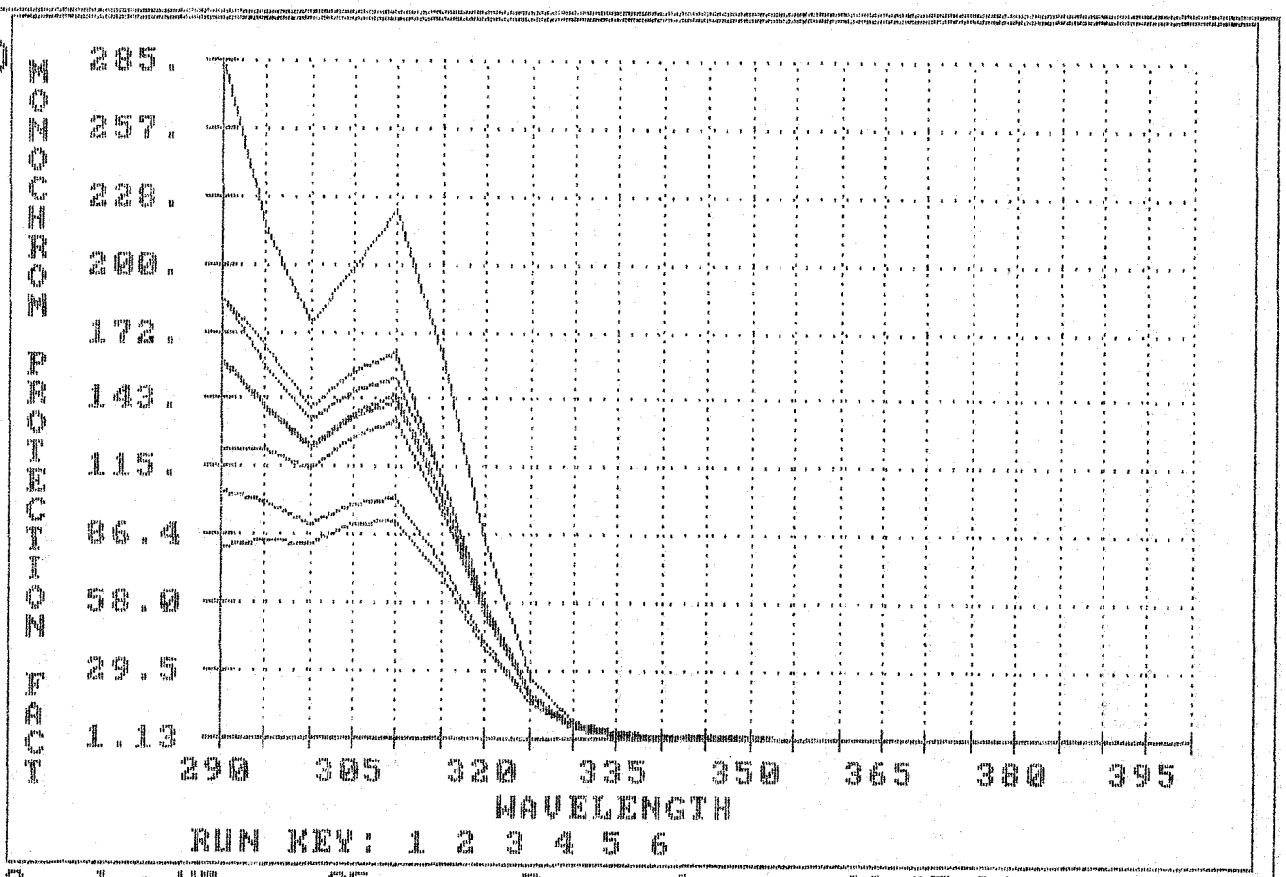
QUANTITY (MPF)	VALUE	S.D.
SPF:	17.2	1.7
UVA/UVB Ratio:	.35	.01
Average UVA PF:	7.2	1.0
Erythemal UVA PF:	5.4	.4

10 — 10
40 NORTH 20 ZENITH

Erythemal Action Spectrum

SPF 290 (Ver. 2.00) by Optometrics USA, Inc.

Lambda	MPF	+/- SD
290	160.8	74.6
295	140.8	48.4
300	123.0	34.3
305	136.5	39.5
310	144.6	47.3
315	103.5	33.6
320	55.5	15.9
325	19.5	4.3
330	6.4	.9
335	3.0	.3
340	2.0	.1
345	1.7	.1
350	1.5	.1
355	1.4	.0
360	1.3	.0
365	1.3	.0
370	1.3	.0
375	1.2	.0
380	1.2	.0
385	1.2	.0
390	1.2	.0
395	1.1	.0
400	1.1	.0



Sample: HT_exp.35 Runs: 6 06/07/00 12:32:42
Thickness: 2.0 ul/cm2 Ref: TRANSPORE Operator: glenn
File: HT_EXP35

QUANTITY (MPF)	VALUE	S.D.
SPF:	14.6	1.0
UVA/UVB Ratio:	.15	.00
Average UVA PF:	6.0	1.3
Erythemal UVA PF:	3.2	.1

10 — 10
40 NORTH 20 ZENITH

Erythemal Action Spectrum

SPF 290 (Ver. 2.00) by Optometrics USA, Inc.

SUNSCREEN STANDARDS TESTED WITH DIFFERENTLY FILTERED SOLAR SIMULATORS

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Abreviations: UV ultraviolet radiation,
SPF Sun Protection Factor,
MED minimal erythema dose,
CIE Committee internationale de l'eclarage,
COLIPA The European Cosmetic Toiletry and Perfumery Association

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SUNSCREEN STANDARDS TESTED WITH DIFFERENTLY FILTERED SOLAR SIMULATORS

Since the development of UV emitting solar simulators, there have been remarkably few research studies reporting sunscreen testing results on differently filtered solar simulators.[1-5] Although most of these studies compare the efficacy of sunscreen standards when tested in 'round robin' experiments.[3-5] There have been three standards for solar simulators which appear to have been written without any detailed information as how products or standards might test using the specific limits proposed.[3-7] In fact few published studies have seriously examined possible differences in sunscreen efficacy under different UV irradiation conditions.[8] There has been only one study published that examined the SPF of a standard and a sunscreen product over a period of several years.(

The purpose of this study is to investigate the SPFs of two SPF 15 standards when tested with solar simulators filtered to meet the acceptance extremes of the only currently accepted solar simulator standard.[3] The investigation examines

the standards using human *in vivo* SPF testing techniques and using *in vitro* predictive techniques.[9]

Materials & Methods:

Materials:

Two sunscreen standards were chosen: COLIPA designated P2 and P3. The P2 standard utilizes Padimate O at 7% and Oxybenzone at 3% as the sunscreens. The P3 standard utilizes Octylmethoxycinnamate at 3%, Butyl methoxydibenzoylmethane at 0.5%, and Phenyl benzimadazole sulphonic acid at 2.78%. P2 and P3 are COLIPA designations of the Standards.

UV Sources:

Two Solar Light Company Solar Simulators were used. Lamp A was filtered with 1 mm WG-320 and a UG-11 visible NIR filter. The total power (250-800 nm) of Lamp A was 65 mW/cm^2. lamp B was filtered with a 1 mm WG-320 plus a 1 mm Pyrex microscope slide but no UG-11 filter. The dichroic mirror in the solar simulator reduced the intensity of visible an NIR. The total power of Lamp B was 146 mW/cm^2. Both solar simulators were measured using spectroradiometric techniques and determined to be within the spectral limits established by the COLIPA Standard. See TABLE 1 and FIGURE 1.

Study Methods: *In Vivo*

The standard FDA or COLIPA sunscreen test requires that a product be applied at an application density of 2 mg/cm^2 and exposed to a graduated series of exposures from a solar simulator on both product protected skin and untreated, adjacent control skin. 24 hours later the MEDs are read for the control skin and the product or standard treated skin.

All studies reported were undertaken within the framework of standard US FDA recommended sunscreen studies. Ten volunteers were chosen with skin types I to III. Each volunteer was treated twice with each sunscreen standard and irradiated once for each standard with each solar simulator. In addition control untreated MEDs were determined also.

Twenty four hours after exposure the sites were graded and results recorded.

Study Methods: *In Vitro*

The transmittance of films (2 mg/cm^2 applied to collagen matrix – lambskin condom) of the P2 and P3 sunscreen standards were measured using an Optronic OL-754 spectroradiometer in transmittance mode. The UV light source was a Solar Light Co solar simulator without either a WG-320 nor UG-11 filters. To estimate the SPF the transmittance was multiplied by the spectrum of solar simulator Lamp A or Lamp B and also by the CIE erythemal action spectrum. The sum of this product spectrum was divided by a product spectrum of either

Lamp A or Lamp B times the CIE erythema action spectra. The ratio is an estimate of Source Spectrum x CIE spectrum divided by Source Spectrum x CIE spectrum x Transmittance Spectrum estimates the MED expected for the source.[10]

Results:

Figure 1 shows the spectra for each solar simulator filtration utilized in this study. Table 1 show that both solar simulators comply to COLIPA standard.

Table 2 show the results of the ten volunteers when tested with the P2 Standard. In addition the mean SPF and Standard deviation are given. A paired student's T test indicate that the SPFs for the two different solar simulator filtrations are statistically different (P=.000020).

Table 2. also shows the results of testing the nine volunteer when tested with the P3 COLIPA standard. In addition the mean SPF and Standard deviation are given. A paired student's T test indicate that the SPFs for the two different solar simulator filtrations are statistically different (P=.0073).

Figure 2 shows the transmittance spectra of P2 and P3. Table 4 compares the estimated in vitro SPF of each standard for each Lamp used.

Discussion:

The P2 standard is expected to be have an SPF of 12.7 with an expected standard deviation of 1.2[3,4] Our results for both solar simulators are reasonably consistent with their reported value. For the standard 1 mm WG-320 filtered solar simulators we observed a 14.9 while with the other 1 mm WG 320 and also filtered with a 1 mm pyrex filter solar simulator the observed SPF was a 10. What is different in our study is that because this is a paired study, both sunscreen standards were tested on the same individuals, we show that these results (SPF 14.9 versus 10.0) were statistically at P.00002. By comparing the two solar simulator spectra in a paired study, we demonstrate that even at relatively low SPF values the specific source filtration makes a difference.

For the other P3 standard, COLIPA reports that a SPF of 15.5 is expected with a standard deviation of 1.5.[3,4] Our 1 mm WG320 filtered system (SPF 14.5) provided results exactly consistent the COLIPA round robin study. The 2 mm WG320 filtered system SPF of 9.4 was significantly under this value. Again for the P3 standard the SPFs obtained for the two solar simulators are statistically different at the P.0073 level. Both the P2 and P3 Standards provide different SPFs when tested with solar simulators filtered differently but within the spectral range accepted by the standard and in compliance to the standard.

In the previously published studies, the earliest work showed that by filtering solar simulators differently different SPFs would be obtained.[1] Collaborative studies such as those provided in the COLIPA Standard and subsequent publication[9] failed to analyze that perhaps different solar simulators produced

different results. In fact when different results were pointed out in earlier submissions to the FDA, when the data was published in the report, the statistical difference observed between the same standards when tested in different laboratories was ignored in the published report.

The magnitude of the SPF differences observed because of solar simulator spectral weighting at the SPF 10-15 level appears to be approximately 50%, The spectra of the two solar simulator used in this study show that the 1 mm WG-320 / 1 mm UG-11 filtered solar simulator not only consistently provided a higher SPF for the standard sunscreen product. The source with a 2 mm WG-320 and without an UG-11 consistently provided lower SPF values for tests with either the P2 or P3 standards. The 1 mm WG320/1 mm UG-11 filtered solar simulator has significantly more UVB radiation than does sunlight and has only about 1/3 or the UVA 1 radiation normally in sunlight. On the other hand, the 2 mm WG-320 filtered solar simulator has less UVB radiation and without the UG-11 filter has all the available UVA-1 emission of the xenon arc.

Regarding the filtration used to obtain the compliance of the solar simulator for the without the UG-11 filter, a 1mm Pyrex microscope slide was used as a secondary filter. Combinations of multiple 1 mm thick filters caused the system without the UG-11 to exceed the limitations of the COLIPA standard. The Pyrex microscope slide was inserted and found to modify the spectrum sufficiently for the spectrum to just remain COLIPA compliant.

The *in vitro* SPFs estimates agree remarkably with those determined by SPF testing. It seems strange that this significant difference between source filtrations has not been observed and commented upon previously.

Conclusions:

Within the framework of the COLIPA standard for solar simulators filtered differently but complying to the standard, when testing standard sunscreens provided different efficacies. The values were statistically different and the difference was approximately 50% in magnitude.

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TABLE 1. LAMP A and LAMP B COLIPA Compliance

	Lamp A	Lamp B	
	WG-320 + UG-11 filter	WG-320 filter+ Pyrex slide	
Total Irradiance (250-800 nm)	6.53E-02	1.46E-01	W/cm²
UVC Irradiance (250-290 nm)	1.18E-06	3.32E-08	W/cm²
UVB Irradiance (290-320 nm)	6.89E-03	4.00E-03	W/cm²
UVA Irradiance (320-400 nm)	5.58E-02	6.23E-02	W/cm²
UVA2 Irradiance (320-340 nm)	1.58E-02	1.14E-02	W/cm²
UVA1 Irradiance (340-400 nm)	4.00E-02	5.09E-02	W/cm²
Visible + NIR Irradiance (400-800 nm)	2.61E-03	8.02E-02	W/cm²
%UVC	0.00%	0.00%	
%UVB	10.55%	2.73%	
% UVA	85.45%	42.53%	
%Visible + NIR	3.99%	54.74%	
Estimated MED (seconds)	39	73.2	seconds
Erythemal Effective Irradiance	5.13E-04	2.73E-04	W/cm²
%COLIPA Effective Irradiance			
<290nm (<1.0%)	0.20%	0.00%	Passed
290nm-310nm (46.0%-67.0%)	61.10%	52.80%	Passed
290nm-320nm (80.0%-91.0%)	89.10%	83.80%	Passed
290nm-330nm (86.5%-95.0%)	94.00%	90.10%	Passed
290nm-340nm (90.5%-97.0%)	95.90%	92.80%	Passed
290nm-350nm (93.5%-99.0%)	97.30%	94.90%	Passed

TABLE 2. SPF P2 and P3 COLIPA SPF Standards

				P2 Standard		P3 Standard	
				SPF	SPF	SPF	SPF
Subject	Sex	Age	Skin Type	Lamp A	Lamp B	Lamp A	Lamp B
SMM	F	61	III	15.00	9.62	<9.60	15.60
MNR	F	24	II	16.00	9.62	12.00	8.00
JTP	M	33	I	15.00	10.00	15.00	8.00
RLT	M	42	III	12.00	10.00	>19.06	7.80
MMR	F	32	I	15.00	10.00	12.00	12.00
TLH	F	21	I	18.75	10.00	15.00	10.00
BSB	M	24	II	12.00	8.00	16.00	6.38
EMM	F	20	III	15.00	10.40	15.00	6.40
JLE	F	28	II	15.00	10.00		
TJT	M	19	II	15.00	12.50	12.19	10.00
	Mean=	30.4		**14.88**	**10.01**	**14.53**	**9.35**
	SD=	12.9		1.91	1.09	2.44	2.97
	n=	10		10	10	8	9

Note: Data < or > has been excluded from statistical analysis and comparisons.

TABLE 3. IN VITRO PREDICTED SPFs STANDARDS P2 AND P3

Solar Simulator / Standard	P2	P3
Lamp A	**14.2**	**13.6**
Lamp B	**10.5**	**10.3**

Note: The SPF obtained from both standards is expected to be 50% higher with Lamp A than with Lamp B. This difference is observed in in vivo testing.

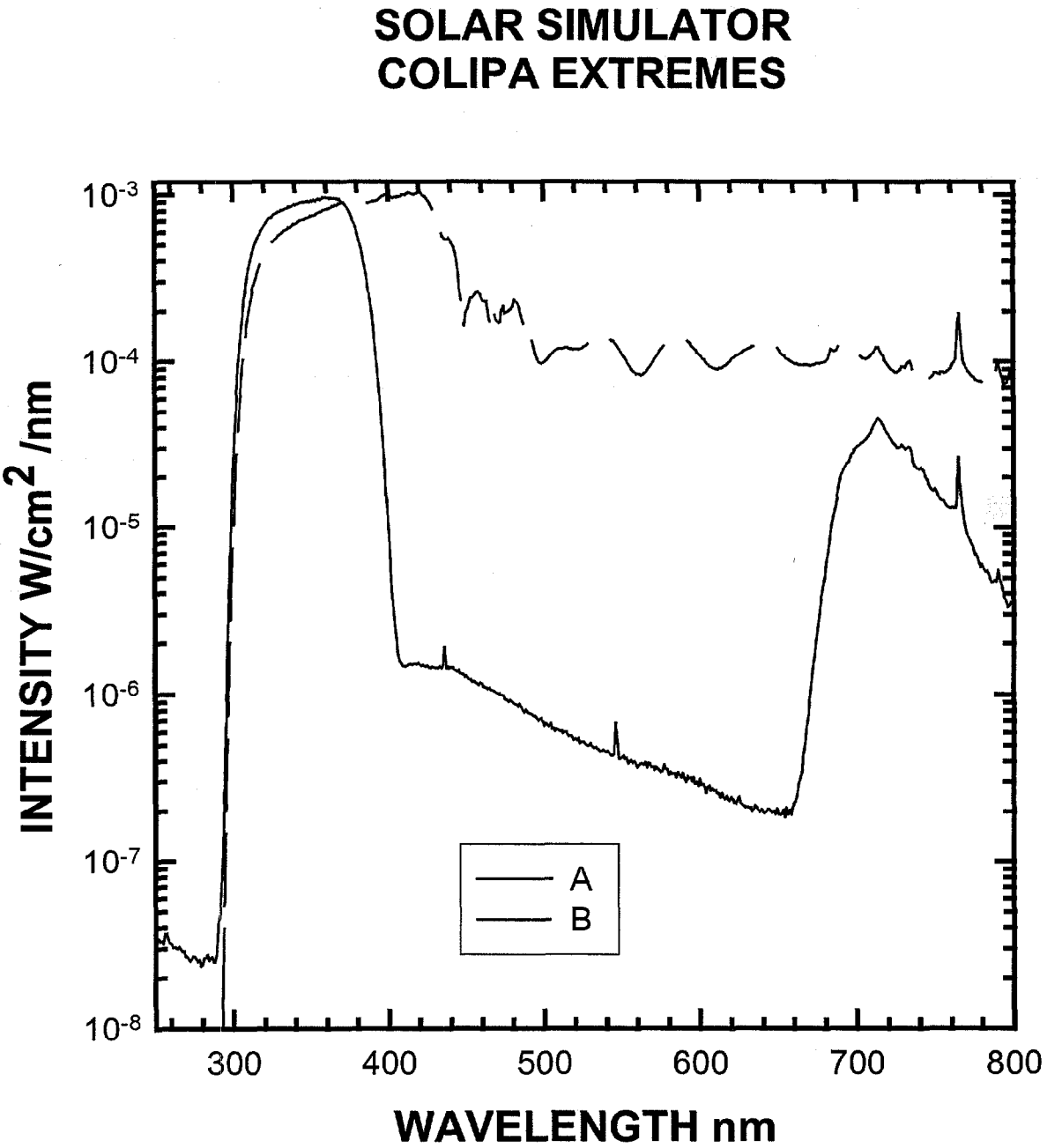
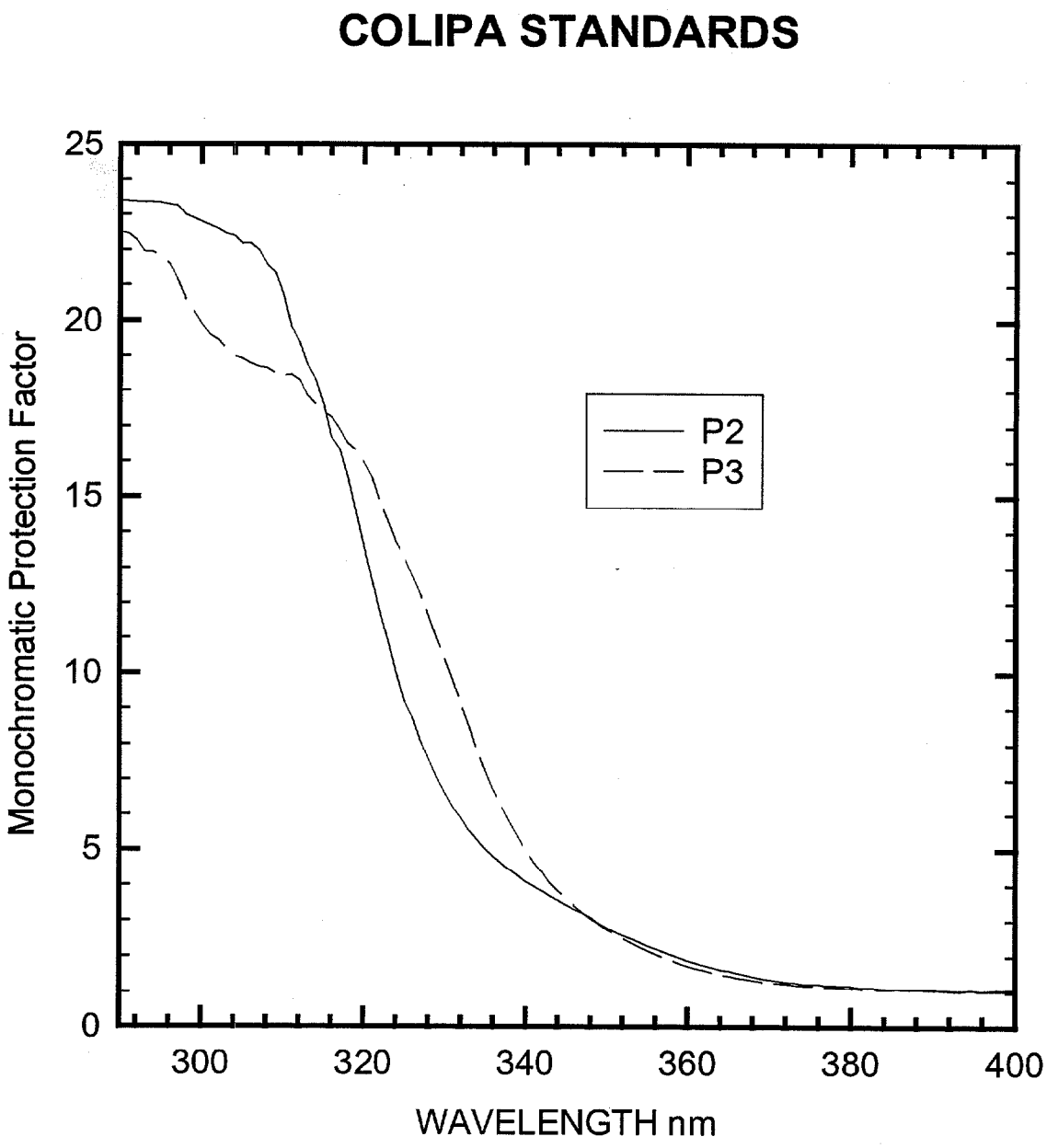


FIGURE 1. STUDY SOLAR SIMULATORS

Solar Simulator A is a standard Solar Light Company filtered solar simulator. Filtration includes dichroic mirror, 1 mm WG-320, and1 mm UG-11. The UG-11 filter clearly removes much visible light but also removes UVA-1 radiation longer than 360 nm. By 400 nm less than 1% of the available light is available. Solar Simulator B has in addition to the WG-320 an added Pyrex microscope slide to remove slightly more of the short wavelength radiation because the removal of the UG-11 causes slightly more short wavelength UVB than COLIPA allows to now be in the beam. Note: while 90% of the visible and near infrared has been removed by the dichroic mirror, there is still a considerable amount. See TABLE 1.

Figure 2. IN VITRO PROTECTION OF STANDARD SUNSCREENS



Appendix 4

Evaluating Same Subject Standard SPF Measurements

Objective

To evaluate the effect of seasons on the standard SPF measurement using subjects who tested multiple times over a twelve-month period.

Observations

Twenty-five (25) subjects who tested SPF products multiple times over a 12-month period were evaluated on the basis of the standard SPF measurement obtained for the test. There were 196 total tests over the 12-month period by these subjects. Equipment and personnel were constant throughout the period covered by the study. As each SPF test is product specific, the standard SPF measurement for the 8% homosalate lotion was used as a control. The standard SPF measurements were tabulated and then grouped into four three-month groups to evaluate seasonal differences in the standard SPF measurement. Statistical evaluation of the SPF measurements revealed that the standard SPF measurement obtained in July, August, and September was lower than that obtained for the other groupings. This grouping was chosen to approximate the period of optimal sun exposure (summer) that could influence MED and therefore standard SPF measures.

Standard SPF Measurement Grouped in 3-Month Intervals

SUMMARY

Groups	*Count*	*Sum*	*Average*	*Variance*
July/Aug/Sep	37	167.39	4.524054054	0.133963664
Oct/Nov/Dec	50	249.87	4.9974	0.398835959
Jan/Feb/march	57	284.44	4.990175439	0.320533897
Apr/May/June	52	260.46	5.008846154	0.374763348

ANOVA

Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	6.767513012	3	2.255837671	7.050814415	0.000160445	2.651638908
Within Groups	61.42848291	192	0.319940015			
Total	68.19599592	195				

Standard SPF Measurement
July 1999-June 2000

	July	August	September	October	November	December	January	February	March	April	May	June
STD. SPF	5	5	4.4	5		6.24	6.24		5	4.4	5	5
STD. SPF						5	5		5	6.24	5	5
STD. SPF		4.4	4.4		5	4.4	5	4.4		4.4	4.4	
STD. SPF			4.4		6.24	6.24			5	4.4		4.4
STD. SPF	5	5		5	5	5	5	4.4	4.4		6.24	5
STD. SPF	4.4	4.4		4.4	6.24	6.24	4.4	5	4.4	5	4.4	
STD. SPF		4	5	6.24	6.24		5	5	5	4.4	5	
STD. SPF	4.4			4.4	5	5	5	4.4	5		5	5
STD. SPF	4.4	5	4		5	5	5	6.24	5	4.4		6.24
STD. SPF				5		4.4	5		5	4.4	5	4.17
STD. SPF	4		4		4.4	4.4		5	6.25	6.24	4.4	5
STD. SPF				4	3.75	5	5		5	5	5	5
STD. SPF		4.4	4		6.24		5	5				5
STD. SPF	4		4.79	4.4		4.4		4.4	4.4		5	4.4
STD. SPF	4.8		4	5		5		4	5.28		4.4	6.4
STD. SPF		5		4.4	5	4.4	6.24	4.4			5	5
STD. SPF		5	4.4	5	5		5	5	5	5	5	4
STD. SPF		5	4.4		5	5	5	5	4.4		5	
STD. SPF				4.4		4.4	5	4.4		5	5	
STD. SPF	4.4		4.4					3.67	4.4		6.25	5
STD. SPF			4.4	5		5	5	5	5			
STD. SPF	4.4				5	4.4		5		5	5	
STD. SPF		5	4.4	5		5	6.24	5	5	6.24	5	
STD. SPF				5	5		6.24	6.24		5	5	
STD. SPF		5	4.4	5				5	5	4.4	6.24	

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